IFPMA

Questions & Answers on Biotherapeutic & Biosimilar Medicines

1. ***What is biotechnology and what is its role in biotherapeutic medicines?***
   Biotechnology is described as the set of methods and processes that allow the modification of living organisms – or their parts – in order to produce goods or services. Mastery of so-called "recombinant DNA techniques" in the 1970s opened a new phase in "molecular" biotechnology, revolutionizing various fields of knowledge. Recombinant DNA techniques essentially permitted rapid ways to engineer DNA in biological systems to make therapeutic proteins in a laboratory. Biotherapeutic medicines today are mainly produced by such recombinant DNA techniques. This means that living organisms are genetically reprogrammed to produce a protein of interest. For example, for many years, insulin dependent diabetic patients had only insulin extracted from the pancreases of animals. In 1982 came the first human insulin produced by recombinant DNA technology using a culture of E. coli bacteria. This insulin is superior in quality to the animal-derived product and is produced in sufficient quantities to meet demand.

2. ***What are biotherapeutic medicines[1] and how do they differ from chemically-synthesized small molecule medicines?***
   Biotherapeutic medicines are medicines whose active ingredients are or are derived from proteins (such as growth hormone, insulin, antibodies) and other substances, and are produced by living organisms (such as cells, yeast and bacteria). They are larger and more complex than chemically-synthesized smaller molecule medicines, and their characteristics and properties are typically dependent on their source living organism and manufacturing process. This complexity makes the full characterization of biotherapeutic medicines particularly difficult. Chemically-synthesized small molecule medicines are instead medicines produced through a step-by-step chemical synthesis process. They are derived from structurally simple chemical compounds with smaller molecular weight compared to biotherapeutic medicines.

3. ***How are biotherapeutic medicines manufactured?***
   Biotherapeutic medicines are made using living systems, usually by re-producing a protein in a living cell (such as bacterial or mammalian cells). The characteristics of a biotherapeutic medicine are strongly dependent on the conditions of the manufacturing process, and it is often said that "the process is the product". In fact, even small changes in the manufacturing can alter the final product – therefore the production process of a biotherapeutic medicine requires well designed, robust, reliable, and well controlled

[1] Biotherapeutic medicines can also be referred to as biologics, biological medicines and biopharmaceuticals.

processes. Good manufacturing practices, validation, and defined specifications are of pivotal importance to ensure the safety and efficacy of these products over time: biotherapeutic medicines undergo approximately 250 in-process tests throughout the manufacturing process[2]. It is in fact the manufacturing process itself that imprints unique characteristics into these products.

4. ***What conditions do biotherapeutic medicines treat?***
   Biotherapeutic medicines benefit more than 350 million patients worldwide[3], treating widespread diseases such as cancer and diabetes, as well as rare illnesses. They have proven to be effective in the treatment of some conditions that are particularly difficult to treat with chemically-synthesized small molecule medicines. Over the past 30 years, medical advances in biotherapeutic medicines have focused on treating many complex chronic diseases – including cancer, diabetes, hepatitis C, and chronic renal failure – as well as less common ones such as hemophilia, Fabry's disease, growth deficiency, multiple sclerosis and Crohn's disease.

5. ***How do biotherapeutic medicines actually work?***
   Biotherapeutic medicines are large molecules often designed to disrupt, trigger or replace complex protein-protein or cell-cell interactions in a patient's body. For example in the case of diabetes, human insulin produced by recombinant DNA technology – the world's first biotechnologically manufactured medicine – acts to replace the missing protein in the patient. Biotherapeutic medicines are thus developed based on a deep understanding of disease biology in the human body, and are targeted to the specific cause or debilitating symptoms of a disease. Chemically-synthesized small molecule medicines, in contrast, are generally less targeted and address less complex mechanisms of action.

6. ***How are the quality, safety and efficacy of biotherapeutic medicines evaluated?***
   Demonstrating, evaluating and monitoring the quality, safety and efficacy of all medicines is important throughout their life cycle. Health regulatory authorities have requirements in place for evaluating such elements, both pre- and post-approval. Companies also have standard operating procedures and good manufacturing practices in place to ensure that only quality, safe and effective medicines are used in the marketplace.

[2] EuropaBio (undated) Guide to biological medicines: a focus on biosimilar medicines
http://www.europabio.org/sites/default/files/report/guide_to_biological_medicines_a_focus_on_biosimilar_medicines.pdf
[3] EuropaBio (undated) Guide to biological medicines: a focus on biosimilar medicines
http://www.europabio.org/sites/default/files/report/guide_to_biological_medicines_a_focus_on_biosimilar_medicines.pdf

With regard to biotherapeutic medicines, more sophisticated tools and techniques – that go beyond those applied for small molecule medicines – are necessary to demonstrate quality, safety and effectiveness in the pre-approval phase. This is due to the complexity of such medicines, to the processes necessary to produce them, and to their potential to cause unwanted immune reactions. Because of the limited number of patients involved in the clinical trial phase, post-marketing surveillance (as part of a pharmacovigilance system) is also a fundamental tool to allow health authorities to continue to assess benefit/risk throughout the life-cycle of a medicine, and potentially detect rare and serious adverse events that were not identified before marketing authorization.
Pharmacovigilance can detect new safety signals related to product quality and/or changes in use and prescription patterns. The World Health Organization (WHO) describes a national pharmacovigilance system "as an obligatory investment in the future public health of the territory"[4]. Maintaining a robust pharmacovigilance system relies on consistent and accurate acquisition, integration and analysis of adverse event data[5]. Without such a strong foundation important safety signals can get hidden, confounded or diluted. While this need for a strong foundation is common to all medicines, it is especially important for biotherapeutic medicines[6].

7. What are biosimilars and how are they different from generic chemically-synthesized small molecule medicines?

A biosimilar is defined as a product that is similar to an already authorized originator biotherapeutic product, with demonstrated similarity to the latter in terms of quality, efficacy and safety[7] assessed through a direct (or head-to-head) comparison. Biosimilars are therefore similar but not identical to their originator medicines of reference. Due to their complex molecular structure and unique manufacturing process, it is impossible for biosimilars to be the exact copy of its reference originator. This fact is not true for chemically-synthesized small molecule generic medicines that are stable molecules with a single identifiable structure, containing the exact copy of the active pharmaceutical ingredient (API) of their reference originator. Biosimilars are also referred to as similar biotherapeutic products, follow-on biologics, and subsequent entry biologics.

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[4] WHO (2006) The safety of medicines in public health programs: pharmacovigilance an essential tool http://www.who.int/medicines/areas/quality_safety/safety_efficacy/Pharmacovigilance_B.pdf

[5] The WHO has created guidelines for pharmacovigilance systems that can be found at the following link http://www.who.int/medicines/areas/quality_safety/safety_efficacy/Pharmacovigilance_B.pdf

[6] Giezen et al. (2008) Safety-Related Regulatory Actions for Biologicals Approved in the United States and the European Union. JAMA; 300(16): 1887

7 According to the WHO Guidelines on the Evaluation of Similar Biotherapeutic Products (SBPs) , biosimilars are "similar in terms of quality, safety and efficacy to an already licensed reference product"

8. **How is it possible to assess whether a given product is a biosimilar to an originator biotherapeutic?**
   Because of their complex nature, biosimilars require distinct regulatory pathways from those applied to generic medicines. The regulatory pathway for a generic medicine is fairly simple and straightforward, requiring only that the API is shown to be identical to that of the originator and that the generic is demonstrated to be bioequivalent to the originator. This approach is not acceptable to demonstrate biosimilarity. For a biosimilar to be approved as such, it is essential that it proves high similarity – meaning the absence of any relevant differences in the studied parameters of interest – to its reference biotherapeutic product (RBP) with respect to quality, efficacy, and safety. This assessment is done through a stepwise exercise, the main objective of which is to demonstrate biosimilarity. These exercises start with a comparison of the quality characteristics of the intended biosimilar against those of the RBP. Once high similarity is demonstrated at the quality level, the assessment continues with comparative targeted pre-clinical and clinical studies having the intention to exclude relevant differences in the safety (including immunogenicity) and efficacy profiles of the biosimilar and RBP. This means that patients can expect a comparable clinical profile between the two medicines.

9. **Are there differences in the manufacturing processes followed by a biosimilar manufacturer from those followed by an originator manufacturer?**
   The production of biologics is complex and may be sensitive to minor variations. Since the manufacturer of an intended biosimilar has no access to the development and manufacturing data of the originator, it will use a different manufacturing method (meaning a different cell line, raw materials, equipment, processes, and process controls). Biosimilar manufacturers have to establish their own process and manufacturing method with appropriate controls. Despite being based upon the same scientific principles, demonstrating similarity between an RBP and an intended biosimilar will require more extensive and comprehensive data than assessing the comparability of an already approved product before and after a manufacturing change.

10. ***What is the regulatory pathway for SBPs?***
    Science-based regulatory standards for medicines are essential to ensure patient safety. Because of this – and given the complex nature of biotherapeutic medicines – SBPs require distinct regulatory standards from those applied to generic medicines. These standards necessitate thorough analytical characterization and quality studies as well as targeted pre-clinical and clinical development programs to show high similarity to the reference innovative biotherapeutic medicine in terms of quality, safety and efficacy.

A scientifically rigorous regulatory approval pathway for biosimilar products should ensure that there are no meaningful clinical differences between a biosimilar and its reference product in terms of quality, safety, and efficacy. Thus, the biosimilar product would be expected to produce comparable clinical results as the reference product. In 2005 the European Medicines Agency (EMA) implemented the first regulatory framework exclusively for the authorization of SBPs[8]. Furthermore, in 2009 the WHO developed guidelines to serve as a blueprint for countries for the development and evaluation of SBPs[9]. The minimum standards outlined in the WHO guidelines were developed to promote a specific pathway for SBPs, while maintaining standards for quality, safe and effective medicines.

11. What are the key considerations for a robust, science-based regulatory pathway for biosimilars?

- Establishment of a regulatory framework that is distinct from that used for generic chemically-synthesized small molecule medicines
- Require that sponsors of the biosimilar select an appropriate RBP approved on the basis of a complete dossier for use in comparative studies
- Require that the proposed biosimilar and the RBP can be demonstrated to share the same mechanism of action (to the extent known), dosage form, strength, and route of administration
- Require that sponsors of biosimilars demonstrate a comprehensive understanding of the physicochemical and biological characteristics of the biosimilar product and RBP through thorough comparative analytical studies
- Require sponsors of biosimilars to confirm high similarity of the proposed biosimilar to the RBP in terms of safety and efficacy through appropriately designed tailored non-clinical and clinical studies
- Require that immunogenicity of the proposed biosimilar be adequately evaluated (i.e. in an appropriate number of patients to permit the detection of differences in the types and rates of immunogenic events) pre-market and also appropriately evaluated post-market, and compared to that of the RBP
- Provide for mechanisms to ensure clear prescribing, dispensing, use and pharmacovigilance of biosimilars once marketed (e.g., clear labeling, unique identifiers, patient and physician education, and an appropriate pharmacovigilance plan)

[8] EMA (2005) Guideline on similar biological medicinal products
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003517.pdf
[9] WHO (2009) Guidelines on evaluation of similar biotherapeutic products (SBPs)
http://www.who.int/biologicals/areas/biological_therapeutics/BIOTHERAPEUTICS_FOR_WEB_22APRIL2010.pdf

12. **What should be considered in assessing whether extrapolation of clinical data from one indication to another is scientifically justified?**
    Where a biosimilar meets the requirements for licensure for one indication of use that has been approved for the originator medicine, it cannot be assumed that it is appropriate to automatically extrapolate clinical data to support a different condition of use. Any extrapolation of clinical data to additional indications in the originator product requires sound scientific justification. This justification requires adequate consideration of:

    - The fact that the mechanisms of action are the same and are sufficiently understood
    - That fact that comparative clinical testing has been done in the setting(s) most sensitive to potential differences in safety, efficacy and immunogenicity
    - The differences in benefit-risk balance between studied and unstudied indications
    - Differences in the patient populations within and between indications.

    The complex issues surrounding extrapolation of indications for biosimilar medicines affirm that the biosimilarity exercise and the regulatory review of a biosimilar application cannot be reduced to a technical, analytical exercise – in-depth understanding and consideration of the above principles, and how they apply to a particular product, is needed to warrant extrapolation. Potential risk to patient safety must be considered when evaluating the justification for extrapolation.